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# PAUL EHRLICH CENTENNIAL

BY

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*Consulting Editor*
E. GRUNBERG

*Memo from*
JOSHUA LEDERBERG

*To:* Jim Hirsch

MS/Ehrlich

Dear Jim

Let me pass on for your personal interest and use, this memo which was sent me by C. H. Browning.

Jim,

Josh

ass. In difficult cases, *e.g.*, with suramin, success may be achieved by the d of intravenous injection of colloidal copper, supposed to act by blocking lls of the RE system, or by very prolonged treatment; or the use of another rug related *qua* resistance may be effective. Acquired drug-resistance withands cyclical transfer and may persist in animal passages even for periods of ears without further contact with the drug. It will not be argued here hether drug-fastness is a mutation, an adaptation, or a continuing ("Dauer") odification. No certain means of abolishing it at will has been discovered, lthough Ehrlich stated that combined treatment inhibited the development f resistance; and some drugs, *e.g.*, suramin, have been considered to be "antiutative." Sometimes relapse strains have lost drug-resistance. Oesterlin[7] ound that treatment with potassium hexatantalate *in vivo* restored sensitiveess to a strain fast to arsenicals.

It was established originally that acquired resistance to parafuchsin involved o increase in resistance to atoxyl or trypan blue, and that this effect is true lso of strains fast to the latter drugs, but that, by successive treatments with he three compounds, a strain could be made fast to them all. A parafuchsinast strain is resistant to certain other triphenylmethane dyes; resistance to he aromatic arsenical drug atoxyl connotes fastness to various atoxyl derivaives ("arsenic-resistance" is a misnomer); and a trypan blue-fast strain resists rypan red, and also suramin, and *vice versa*. In the last instance, the chemical similarity of the compounds is not of a very close kind. The independence of resistance between these classes of drugs was the basis of Ehrlich's "therapeutic sieve." Even more arresting was the fact that resistance to trypaflavin (diaminoacridine derivative) or to other orthoquinonoid dyes and to the atoxyl class was mutual. Acquired drug-resistance has been used for analyzing the characters of chemoceptors, and more will be said of this procedure later. In the case of the pathogenic trypanosomes, practically no indications exist that insusceptibility to a drug may arise from their acquiring power to detoxicate the trypanocide. It must be added that this summary is a general outline from which many interesting details have been omitted.[8] Drug-resistance has been applied in genetic study: a mixture of two drug-resistant strains derived from the same original *T. brucei* was propagated in mice over repeated passages without causing any fusion of characters.(Browning).

Drug-resistance is a serious complication of chemotherapy. But it is not an invariable consequence of repeated treatment. Schnitzer[8] noted that unsuitable dosage with inadequate amounts of drug may lead to supersensitiveness of the strain. It has also been shown that the immunity reaction involved in the relapse procedure hinders the development of drug-resistance. With *T. congolense* in mice, the treatment of repeated relapses by the same dose of a phenanthridine drug resulted in the cure of as great a proportion of animals in the long run (up to a 20th relapse) as were cured initially by the same single dose.[2] On the therapeutic-sieve principle, Ehrlich advocated combined treatment with different classes of drugs, which had proved effective when Laveran originally used trypan red and arsenious acid to cure infections which could not be cured by either drug alone. However, combined treatment, although established experimentally in certain cases, has not been adopted to any extent